

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of : KNIPE ET AL.  
Serial No : 08/278,601  
Filed : July 21, 1994  
For : HERPESVIRUS REPLICATION DEFECTIVE MUTANTS  
Art Unit : 1645  
Examiner : Caputa, A.

Assistant Commissioner for Patents  
Washington, D.C. 20231

**SHOWING PURSUANT TO 37 C.F.R. §1.608(b)**

Sir:

There is basis upon which applicant is entitled to a judgement relative to the patentee of U.S. Patent No. 5,665,362 with respect to the subject matter of the following proposed Count.

A vaccine comprising a pharmaceutically acceptable excipient and an effective immunizing amount of a mutant herpesvirus, said mutant herpesvirus containing a genome in which a viral gene encoding a protein which is essential for production of infectious virus has been deleted or inactivated, wherein said mutant virus is able to cause production of infectious new virus particles in a recombinant complementing host cell expressing a gene which complements said essential viral gene, but is unable to cause production of infectious new virus particles when said mutant virus infects a host cell other than said recombinant complementing host cell, for prophylactic or therapeutic use in generating an immune response in a subject infected therewith.

In particular, applicant reduced to practice the invention of the proposed count prior to September 25, 1990.

The invention defined by the proposed Count is the sole invention of David Knipe. In this respect, the invention defined by the proposed Count was originally disclosed in U.S. application serial no. 07/922,912 filed July 31, 1992, now abandoned, filed only in the name of David Knipe.

A continuation-in-part application, U.S. application serial no. 08/179,106, was filed on January 10, 1994 which added and claimed additional subject matter as to which Robert Finberg and George Siber made inventive contributions.

Declarations of Robert Finberg and George Siber enclosed herein indicate that David Knipe is the sole inventor of the subject matter defined by the proposed Count.

Accordingly, the declarations directed to demonstrating a reduction to practice of the subject matter of the Count identify David Knipe as the sole inventor.

The Declarations demonstrate that the subject matter of the proposed Count was conceived and reduced to practice in the United States prior to September 25, 1990.

The invention was reduced to practice by demonstrating that two different mutant herpesviruses (one mutated in the ICP8 gene and the other in the ICP 27 gene 1 protected mice against a lethal dose of wild-type herpesvirus, HSV-mP. The mutant herpesviruses that provided such protection were not capable of producing additional virus in cells other than cells that complemented the defective genes. In particular, the mutated viruses used in these experiments consisted of one herpesvirus containing a deletion mutation in the gene that expresses ICP8, known as mutant d301; and the other herpesvirus containing a nonsense insertion mutation in the gene expressing ICP27, known as mutant n504R.

The production of a mutated herpesvirus that was successfully used for protection is corroborated by the Declaration and notebook pages of Stephen A. Rice. As stated by Dr. Rice and as shown in his notebook, in the United States prior to September 25, 1990, an ICP27 mutant

herpesvirus that was replication defective was produced. The ICP27 mutant herpesvirus produced virus in cells that complemented the mutant gene, however did not produce virus on normal cells lacking the mutated ICP27 gene.


The production of a mutated herpesvirus that was successfully used for protection is also corroborated by the Declaration and notebook pages of Min Gao. As stated by Dr. Gao and as shown in the notebook, in the United States prior to September 25, 1990, an ICP8 mutant herpesvirus that was replication defective was produced. The ICP8 gene internal deletion mutant herpesvirus produced virus in cells that complemented the mutant gene, however did not produce virus on normal cells lacking the ICP8 gene.

The reduction to practice is further corroborated by the Declaration of Robert Finberg (a non-inventor with respect to the subject matter of the proposed Count) and the notebook pages of Lien Huong Nguyen in which the work constituting the reduction to practice were recorded. As stated by Dr. Finberg and as shown in the notebook pages of Dr. Nguyen, in the United States prior to September 25, 1990, the ICP 27 (n 504R) and ICP 8 (d301) mutant herpesviruses provided a protective immune response in animals to challenge with wild type herpesvirus. In particular,  $10^6$  pfu of replication-defective viruses, (those containing mutations in the genes encoding ICP8 or ICP27), were injected into mice, and then challenged with a lethal dose of  $10^8$  pfu live wild-type HSV-1 virus. The mice that received the mutants had 100 % survival rates whereas for the control mice that did not receive mutant virus one of nine survived. Thus the experiments demonstrated that replication defective mutants of HSV-1 when injected in mice protected against lethal infection whereas the majority of mice injected with control material and subsequently challenged with wild type virus, died.

Applicants have provided proof of prior reduction to practice of species encompassed by the generic invention of the proposed Count. Such evidence has been held to be enough evidence to prevail with respect to priority for purposes of an interference. *Squires v. Corbett* 194 USPQ 513, CCPA.

Applicants submit that the evidence presented herewith demonstrates that applicants are prima facie entitled to a judgement regarding priority of invention and that an interference should be declared.

The Declarations of David Knipe, Stephen Rice , Min Gao, and Robert Finberg, as well as the documentary evidence in the form of laboratory notebook pages, presents a prima facie case that applicant would prevail in an interference proceeding with U.S. Pat. No. 5,665,362 based on the proposed Count (the proposed Count is identical to claim 1 of U.S. Pat. No. 5,665,362 ) in that there was a reduction to practice in the United States prior to September 25, 1990, the earliest priority date set forth in the '362 patent.

<b>FIRST CLASS CERTIFICATE</b>	
I hereby certify that this correspondence is being deposited today with the U.S. Postal Service as First Class Mail in an envelope addressed to:	
Assistant Commissioner for Patents Washington, DC 20231	
 Raina Semionow, Esq.	<u>9-8-98</u> Date

Respectfully submitted,



Raina Semionow, Esq.  
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